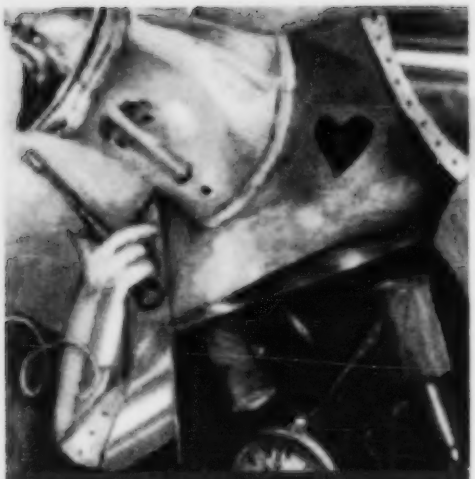
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

WINTER 2001

research news

Heritage researchers go as far as the Amazon in the quest to solve gut ailments.

GUT *feelings*



AHFMR Mission

AHFMR supports a community of researchers who generate knowledge that improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund basic, patient and health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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Production Notes

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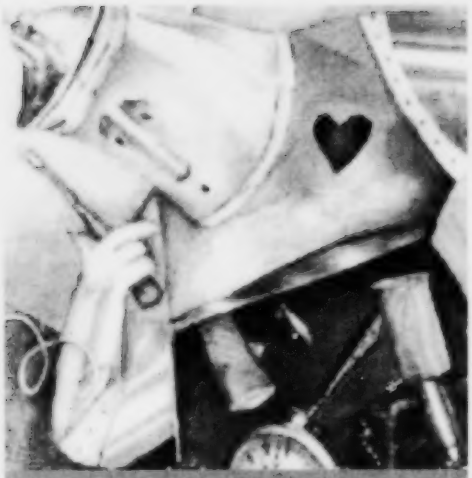

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research

Remarkable advances in human and domestic animal health—vaccines, treatments for cancer, heart disease, diabetes for example—have been made possible by the contributions of animals to research. Yet there are those in our society who are uncomfortable with the use of animals in research, and whose views range from expressing the need for caution to wanting outright abolition of the practice. Quite apart from furious debate it engenders, it is no easy task for scientists to engage in animal research.

"The care and use of animals in research, testing, and teaching is an immense responsibility for all involved, and must be performed with the utmost respect and dignity," emphasizes Dr. David Neil, University Veterinarian in the Office of the Vice-President Research at the University of Alberta. Dr. Neil has worked as a laboratory animal veterinarian in the U.K., U.S.A. and Canada for almost four decades. He is one of an impressive team of veterinarians, animal scientists and animal technologists who works with the entire research community in developing an animal care and use program at the University of Alberta.

The Canadian Council on Animal Care (CCAC)—the national body which sets overall guidelines for animal care and use in science and oversees animal care and use in Canadian private, governmental and academic institutions—has held up this program as a benchmark: The University of Alberta is a recipient of the CCAC Certificate of Good Animal Practice®.

Dr. Clément Gauthier, Executive Director of the CCAC, explains that "the CCAC applies the principle of the 'Three R's': to replace animals with other methods whenever possible, to reduce the number of animals used in research, and to refine techniques through its programs of Guidelines Development, Assessment and Education."

Researchers who use animals must pass rigorous reviews that scrutinize every aspect of the proposed investigation, "from the validity of the science, the necessity of using animals, the species of animal proposed, to the care of the animal at every stage of the research," says Dr. Neil. At the University of Alberta for example, approval is needed for proposed research protocols from one of three university committees whose composition and functioning is defined by the CCAC.

Made up of scientists, a veterinary member, as well as members from the community at large, each committee in turn reports to an overarching committee, the University Animal Welfare and Policy Committee, as mandated by the Agriculture, Food, and Rural Development Ministry of the provincial government. Funding from such agencies as AHFMR and CIHR hinges on this review and approval process. If approval is obtained, the researcher must submit annual reports that specifically address the care and handling of the experimental animals. The CCAC assesses research at Canadian

Page 2 ▸

universities and conducts on-site triennial assessments of facilities and reviews procedures at each institution.

Even with these strict standards ensuring top care, the CCAC wants to formalize education for animal users. The organization recently introduced the National Institutional Animal User Training Program, which will require mandatory participation of all animal users as of January 2003. The Program, which the University of Alberta has already initiated, involves the ethical and practical considerations related to animal care and use. It also familiarizes researchers with all the regulatory bodies at university, provincial and federal levels.

The use of animals in research will not wane in the age of genetics. Sequencing animal and human genomes offers vast potential to improve health once scientists can decipher what genes and their products do.

Fifteen years ago we were in pretty poor shape – lots of things to be done, and nowhere satisfactory to do them.

A critical part of that process involves animal testing for the development of new therapies. "The ethically driven concerns posed by science and technology today have never been more profound and complex" says Dr. Neil. This was foreseen by the University Animal Policy and Welfare Committee when, in the late 1980s, it identified the need for an annual forum for the scholarly review of the ethical issues involved.

Thanks to a bequest from the late Louis D. Hyndman Sr., who had a lifelong concern for animal welfare, the University of Alberta is a leader in this area. The Louis D. Hyndman Sr. Lecture and Awards is an annual day-long event, open to the public, that brings in distinguished guest speakers to address contentious aspects of animal welfare of current relevance nationally and internationally. The Awards are presented to scientists and technicians who have been selected by the University Animal Policy and Welfare Committee from peer nominations for having made outstanding contributions to improve the welfare of animals used in research, teaching and testing. Mr. Hyndman was also instrumental in passing the Animal Protection Act in 1967 (which was revised in 1989) that made Alberta a world leader in animal protection legislation at that time.

Dr. Neil points out that "fifteen years ago we were in pretty poor shape – lots of things to be done, and nowhere satisfactory to do them. AHFMR funded the development of substantial, state-of-the-art animal research facilities, which had us right on track by the early 1990s. And our facilities are still singled out as excellent. Good animal care and good science go hand in hand."

new feature

You might notice a new feature of AHFMR Research News in this edition. We've added details on recent papers published by the researchers we feature. Due to space, we've had to keep this list very short—in many cases it's just one paper. However, the idea of listing publications came from one of our readers, a Medicine Hat physician. Like many doctors, he appreciates the public aspect of our stories, but feels he has enough professional reading to do just to keep on top of medical information that he has scarce time to read anything unrelated. Hence, his suggestion that we reference the featured research with recent publications in peer-reviewed scientific and medical journals that doctors routinely read.

Why do I bring this to your attention? Because all of us involved in bringing you this magazine welcome your suggestions and comments on anything we can do to give you a better reading experience. Please feel free to e-mail, write, phone, or fax us at AHFMR. The contact info is listed on the inside front cover.

All the best for a healthy 2001.

Kathleen Thurber
Managing Editor

Fear of falling

Most of us know an older relative or friend who has experienced a nasty fall or worries about falling. When the worry becomes an overwhelmingly anxious state, it's a clinical condition described as "fear of falling," says Dr. Lesley Brown, a University of Lethbridge health researcher.

"Falling is a real problem, but fear of falling is even bigger" in terms of the condition's prevalence, she says. The fear can start limiting people's activities as early as age 45. Dr. Brown, an Assistant Professor of kinesiology, is studying age-related changes in balance in comparison groups of elderly adults and young university students. The elderly group includes about 40 residents of the Lethbridge area—an equal number of healthy and generally very active men and women—ranging in age from 60 to 90.

In one phase of Dr. Brown's research, participants stand at the very edge of a metal platform raised about two metres off the floor. Wearing a loose-fitting safety harness, they perform simple tasks that challenge their balance such as leaning forward as far as possible. They stand on a "force plate" that measures how much their body shifts and adjusts.

"What I'm interested in describing is simply how that threat to balance changes the way they control their balance or the way that they orient their body," Dr. Brown explains. In another phase of the study, participants walk along a wooden beam 20 centimetres wide and eight metres long, raised 20 centimetres off the floor. Six infrared cameras film each person's movements while walking and standing. Tiny sensors attached to the body measure muscle activity (such as contraction), and heart and perspiration rates.

Dr. Brown is also investigating how participants direct their attention toward controlling balance, including when they're given a simultaneous cognitive task such as a verbal brain teaser. Her research shows that young and elderly participants alike adjust their posture when faced with fear of falling. Both groups have elevated heart and perspiration rates, indicating anxiety. Young and elderly also adjust their gait in the walking study, proceeding slowly along the beam and taking shorter strides.

Significantly, both groups appear to direct an equal amount of attention toward controlling balance. That might not be a good strategy for older folks, since cognitive resources tend to decrease with age, Dr. Brown notes. Seniors often fall in the home when a grandchild or a pet suddenly darts in front of them. "So if they're caught off guard, they might not be able to react as quickly because they're so focused on trying to maintain their balance..."

Dr. Brown's studies to date suggest that postural rigidity and "hyper-awareness" induced by fear of falling may be detrimental in preventing falls. "It suggests that we might need to pay more attention to fear of falling in the rehabilitation [programs] for falls."

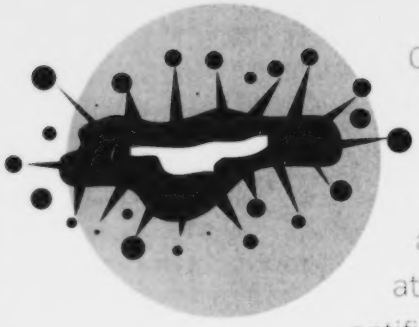
Dr. Lesley Brown's work is supported by the Health Research Fund administered by the Alberta Heritage Foundation for Medical Research on behalf of Alberta Health and Wellness. *She is an Assistant Professor in the Department of Kinesiology and Physical Education at the University of Lethbridge.*

DE JOURDAN PHOTOGRAPHY

Recent publications:

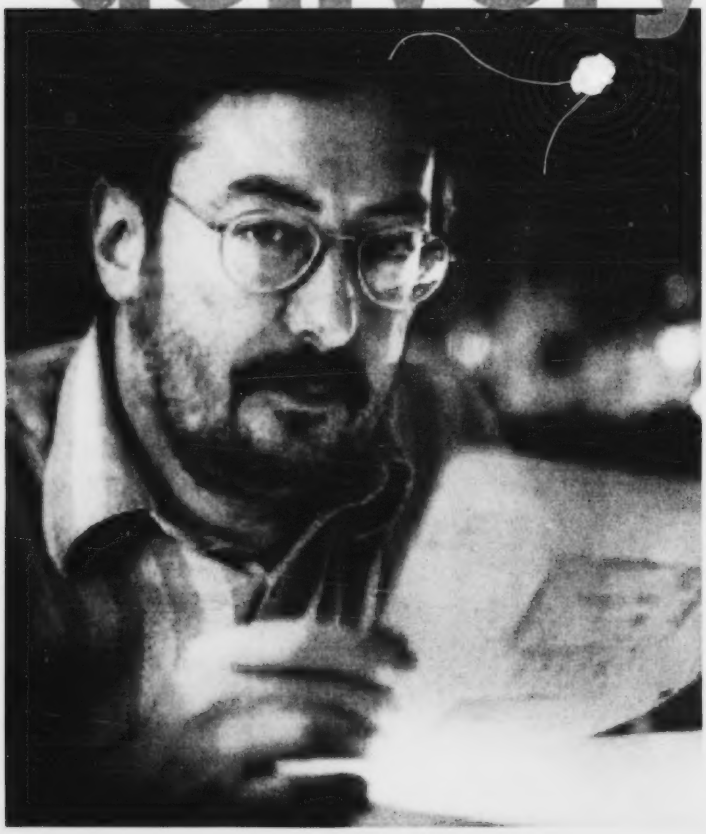
Ranklin JK, Woollacott MH, Shumway-Cook A, Brown LA. Cognitive influence on postural stability: a neuromuscular analysis in young and older adults. *Journal of Gerontology: Medical Sciences* 2000; 55A: M112-M119.

Brown LA, Woollacott MH, Shumway-Cook A. Attentional demands and postural recovery. *Journal of Gerontology: Medical Sciences* 1999; 54A: M165-171.



One of the biggest mysteries in cancer research is why some cancer cells live even after killer T cells attack them. Years of scientific inquiry on the part of a research team led by Dr. Chris Bleackley have gone into finding an answer. The team has identified a receptor on normal cells that allows the cells to be killed when they become dangerous. This molecule is often lacking on cancer cells, allowing them to survive a killer T cell onslaught.

a deadly delivery



Killer T cells (also known as cytotoxic T lymphocytes) are the immune system's response against body invaders that weaken it and cause diseases. Their job is to attack and destroy a cancer cell or a bacteria-or virus-infected cell. Although what killer T cells do has been known for years, it wasn't until a series of key discoveries by Dr. Bleackley's lab that the world found out how they do it. Those discoveries, combined with his recent findings, bring a whole new direction not only to cancer research, but to the treatment of autoimmune diseases and prevention of the transplant rejections.

Return to sender

In 1986, Dr. Bleackley pinpointed in killer T cells a pair of toxic proteins, called granzymes, that trigger cell suicide. These granzyme proteins are the active ingredients in what he calls the killer T cell "letter bomb". Nearly ten years later, the biochemist discovered that when killer T cells deliver granzyme to the infected cell it activates another protein, called caspase 3, that causes the cell to die. This process is known as apoptosis, or programmed cell death. In his latest research findings, Dr. Bleackley has discovered that granzyme is delivered to the doomed cell through a specific receptor "mailbox". The fact that the receptor is the same one that has been identified as a tumour suppressor by other researchers suggests that some cancer cells survive killer T cell attacks by maintaining fewer receptors to receive the granzyme protein. Without a mailbox, the killer T cells have nowhere to deliver their deadly packages.

This discovery points the way to potential new cancer treatments. Dr. Bleackley notes: "Knowing the trigger that allows cancer cells to dodge death means researchers can now focus on how to get the cells to make more receptors or find a way to convince the ones that are there to accept the killer T cells," he explains. "It's the perfect target for drug therapies."

A team effort

His research team's success was built on the work of Heritage-funded students who have worked in the area for a number of years and key collaborations with other Heritage researchers, Dr. Bleackley says. "The Heritage Foundation has played an important role throughout this process. The students doing the studies—Dr. Bruce Motyka, Dr. Alison Darmon, and Dr. Michael Pinkoski—were all Heritage-funded." Heritage researcher Dr. Greg Korbutt, a member of the diabetes islet-cell treatment research team, performed experiments that gave insight into new treatment options for autoimmune diseases and organ transplant rejection. Dr. Bleackley credits another Heritage colleague, Dr. Charles Holmes, with providing a unique enzymatic system that gave valuable clues "to what the receptor really was."

Dr. Chris Bleackley is a Heritage Scientist and a Professor in the Department of Biochemistry in the Faculty of Medicine and Dentistry at the University of Alberta. He is also a Canadian Institutes of Health Research (CIHR) Distinguished Scientist, and a Howard Hughes International Research Scholar. Dr. Bleackley receives additional funding from the National Cancer Institute of Canada.

Recent publication:

Motyka B, Korbutt G, Pinkoski MJ, Heibein JA, Caputo A, Hobman M, Barry M, Shostak I, Sawchuk T, Holmes CF, Gauldie J, Bleackley RC, Mannose 6-phosphate/insulin-like growth factor II receptor is a death receptor for granzyme B during cytotoxic T cell–induced apoptosis, *Cell* 2000:103: 491-500.

Media storm

He knew he would receive some attention for his truly ground-breaking discovery of how cancer cells avoid death even after our immune system attacks them. So Dr. Bleackley wasn't surprised when the local daily newspaper called for an interview after his paper was published in *Cell*, a prestigious international journal. "The article appeared and then nothing happened," he says. "Then a national paper called a few days later. I figured, you know, they'll just write this story and it will get buried in the middle of the paper," he says modestly. However, the next morning he was in for a "rude" awakening. "My wife, who goes out to work very early in the morning, saw the paper as she was leaving and shouted up the stairs, 'You're on the front page!' I went running downstairs and sure enough there was the headline across the top of the newspaper," Dr. Bleackley laughs.

But the media attention wasn't to stop there. By the time he finished teaching later that morning, word of his discovery had spread and "all hell broke loose," Dr. Bleackley says. His office answering machine was full of messages from television and radio stations and newspapers around the world wanting to talk to him. It wasn't long before they descended on his lab for interviews.

While most of the ensuing media coverage was positive, a few stories might have given the impression that he'd found a cure for cancer, Dr. Bleackley explains. "That was a definite down side to this experience," he says soberly. "I had several calls from people with absolutely tragic stories. They either had cancer themselves or had a loved one with cancer, and they were desperate to lay their hands on any kind of treatment. You don't want to give people false hope but you want to be sensitive to their situation. While this discovery has enormous potential, I can't emphasize enough that we are still five to ten years away from seeing any clinical application of it."

Reflecting on his recent fame, Dr. Bleackley takes all of the media attention in stride. "So I was famous for a week or so and now it's all subsided and I'm back to teaching and doing my research," he says with a smile and a shrug of his shoulders.

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Exploring breathing control

Few events are as eagerly awaited as a newborn's first cry—the signal that an infant has successfully made the transition to breathing on its own. But the statistics of sudden infant death syndrome (SIDS) show that the ability to breathe independently is no guarantee that breathing control can be maintained. Every week three babies in Canada die of SIDS, the number one cause of death in infants between the ages of one month and one year, and infants born to mothers who smoke are at increased risk for the disorder. This link between smoking and SIDS is cause for concern. Statistics from the Alberta Alcohol and Drug Abuse Commission indicate that 48% of women aged 15 to 24 years are cigarette smokers, up from 29 percent in 1990.

As a pediatrician with further specialization in diseases of the newborn, Dr. Shabih Hasan is particularly interested in breathing control in the fetus and newborn. His research explores how breathing control is established and maintained, and how it is involved in disorders such as apnea (in which the infant stops breathing intermittently while sleeping) and SIDS. He also studies the effects of smoking on the developing fetus. "A preliminary work suggests that cigarette smoke and nicotine exposure affect factors in the brain stem which are involved in breathing regulation," says Dr. Hasan, who is an Associate Professor in the Department of Paediatrics at the University of Calgary.

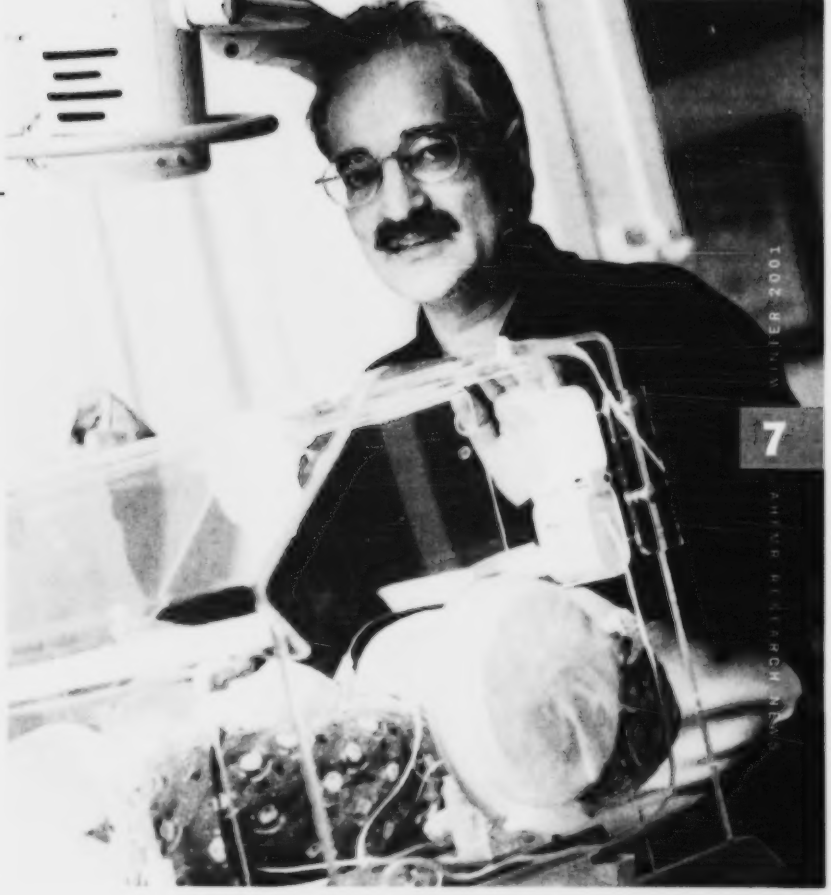
Nerve connection

Dr. Hasan's research looks specifically at the role of the vagus nerve, the longest and most extensive of the nerves originating in the brain, in breathing regulation. The vagus nerve supplies a number of the body's major organ systems, including the upper airway, lungs, heart, and gastrointestinal tract. Vagal afferents, the nerve fibres that carry vital messages about those organs to and from the brain, tell the brain what depth and frequency of breathing is required.

Dr. Hasan and his group have determined just how important the vagal afferents are in establishing breathing control at birth. "Prior to birth, the placenta and the mother get oxygen to, and remove carbon dioxide from, the fetus. After birth, the lungs of the newborn have to start and maintain that gas exchange. What we have found is that if the vagal nerve is severed before birth, the newborn is unable to establish effective gas exchange and breathing."

The researchers looked at four possible causes of respiratory failure in the animals whose vagal nerve had been severed. They initially speculated that these animals might not be experiencing the normal increase in blood flow to the lungs that occurs at birth and is critical to newborn survival; however, this was not the case. They found no abnormalities in the surfactant system, which helps the alveoli, the tiny air sacs in the lungs, to remain open so that oxygen can be absorbed into the bloodstream and carbon dioxide exhaled through the lungs. And there was not sufficient fluid in the lungs (pulmonary edema) to cause respiratory distress. This led the group to focus on the fourth possible cause—atelectasis, a gradual collapse of the air sacs in the lung.

Dr. Hasan describes atelectasis as "de-recruitment" of the lung air sacs—and the vagal afferents clearly play a role in the process. Because the vagal afferents are not communicating with the brain, the air sacs are not getting the message that they are needed. "If the message hasn't been sent by the vagal afferents,"



says Dr. Hasan, "the brain has no idea of lung volume. It isn't able to regulate an appropriate rate, depth and rhythm of breathing. This leads to de-recruitment and, progressively, to respiratory failure."

Smoking and developing lungs

To show how cigarettes might be involved in these breathing problems, Dr. Hasan and his fellow researchers have established two models—one for cigarette smoke and another for nicotine delivery. He credits his graduate student, Svetlana Farkas, with the painstaking work involved in establishing the precise dose of cigarette smoke required to mimic human smoking and to match the concentrations of nicotine and carbon dioxide that are reached. The model's other strength, says Dr. Hasan, is that it provides "nose only" exposure. This ensures that the smoke is evenly distributed. Using this model, the group found that the effects of smoking on the rat fetus were similar to those observed in humans.

The group then developed a model based on continuous infusion of nicotine, to measure the specific roles of nicotine and cigarette smoke. This continuous infusion has a very different impact than does normal cigarette smoking. "Because cigarette smoking is addictive, people regulate their intake," says Dr. Hasan. "When you look at the results in normal cigarette smoking, you get peaks of nicotine. But when the nicotine is being administered continuously, you don't see the effects of that sharp peak.

"It's interesting to note that cigarette smoke leads to a decrease in the fetal weight, whereas nicotine has no such effect," he adds. "This suggests that it is components other than nicotine that impair fetal growth. Nicotine is a very important ingredient—but it's still only one of over 4000 chemicals found in cigarette smoke."

Dr. Hasan and his group's next step is to investigate the effects of prenatal cigarette smoke and nicotine exposure at the organ system, cellular and molecular levels. Monitoring sleep and breathing with state-of-the-art equipment, they will also begin studying the control of breathing in pre-term and term infants in research performed at the bedside.

The brain has no idea of lung volume. It's the vagal nerve that regulates rate, depth and rhythm of breathing.

Dr. Hasan is a Heritage Medical Scholar and Associate Professor in the Department of Pediatrics in the Faculty of Medicine at the University of Calgary. He is also funded by the Canadian Institutes for Health Research (CIHR) and through studentship awards from the Canadian Foundation for the Study of Infant Deaths. A recent addition to his research team is Dr. Elizabeth Wilson, a postdoctoral fellow sponsored by the CIHR, who is investigating infant care practices among aboriginal peoples, where the incidence of SIDS is several times higher than in the non-aboriginal population.

Recent publication:

Hasan SU, Lalani S, Remmers JE. Significance of Vagal Innervation in Perinatal Breathing and Gas Exchange. *Respiration Physiology* 2000; 119: 133-141, 2000

Helping children to get a good night's sleep

So you think sleep apnea is strictly an adult problem? Think again.

Almost 3% of children also suffer from the disorder. Hundreds of times throughout the night, their breathing may become obstructed, preventing them from getting the sleep they need to grow, learn, and stay healthy. A recent study showed that children in the lower tenth percentile of their class often had obstructive sleep apnea, and that treatment for it improved their school performance.

Dreaming to breathe

Obstructive sleep apnea is of particular concern in children because they dream so much. "When we're dreaming, the various muscles that hold the throat open are very relaxed. They're almost completely paralyzed," explains Dr. Val Kirk, a pediatric respirologist at Alberta Children's Hospital in Calgary. "In children, the airways may become so small that air can't flow through properly. As adults, we're lucky if we're dreaming for 10 to 15 percent of the time we're asleep, but children may spend half their sleep time dreaming. This is a sizable amount of time when their breathing may be obstructed."

The most common cause of sleep apnea in children is enlarged tonsils and adenoids, and removing them will usually solve the problem. But surgeons are troubled by the risk of serious bleeding in as many as 3% of patients between seven and ten days after the surgery, which is especially dangerous for children who can't get to the hospital quickly. "That's why we want to be very sure we have the correct diagnosis before we recommend surgery," says Dr. Kirk. That diagnosis is currently made by an overnight sleep study in the hospital sleep laboratory; ideally, it would be done in the child's home.

Detecting children's sleep apnea

Working with the University of Calgary's internationally-known sleep specialists Drs. John Remmers and Ward Flemons, and engineer Eric Hajduk of SagaTech Electronics, Dr. Kirk has helped to adapt the testing device the team developed, the SnoreSat Sleep Recorder, for use with children. The team has added two channels that address the differences between child and adult sleep apnea. One of these channels compensates for children's restlessness during sleep, which can cause false readings in their oxygen saturation levels. The other detects when the child's breathing is only partially obstructed, since children with sleep apnea usually don't stop breathing altogether.

The children undergo one night of investigation in the sleep lab and two at home with the smaller SnoreSat monitor. "We're trying to figure out if we can make the diagnosis by combining the results of the SnoreSat with the results of our physical examination and medical history," she says. "Even though we do what we can to make it more welcoming, the sleep lab is an intimidating environment for a small child. We're attempting to determine if it's feasible to study the children in their own homes."

Children may spend half their sleep time dreaming and that's when their breathing may be obstructed.

Dr. Kirk wants to get the message across early about the importance of good sleep hygiene to our general health. "Children are taught how important it is to exercise and eat well," she says, "but they don't get any education about sleep hygiene. It doesn't make any difference how much exercise you get or what you eat if you're not getting good sleep." She and her fellow researchers are helping children with sleep apnea to do just that.

Dr. Valerie Kirk's research is supported by the Health Research Fund, administered by AHFMR on behalf of Alberta Health and Wellness. She also receives support from the Alberta Lung Association, the Calgary Regional Health Authority, the Canadian Institutes of Health Research (CIHR), and the Alberta Children's Hospital Foundation.

Recent publications:

Kirk VG, Morielli A, Brouillette, RT. Sleep disordered breathing in children with myelomeningocele: the missed diagnosis. *Developments in Medicine and Children's Neurology* 1999;41: 40-43.

Kirk VG, McFadden S, Boag G, Pinto A. Sigalet DL, Leiomyoma of the esophagus associated with bronchial obstruction owing to inflammatory pseudotumor in a child. *Journal of Pediatric Surgery* 2000; 35(5): 771-774.

Sleep problems and child development

In other research, Dr. Kirk is working with a child psychologist and an interested pediatrics resident to look at the effects of sleep apnea on learning and behaviour. Whereas adults with sleep apnea become sleepy during the daytime, children are more likely to be cranky. They have difficulty concentrating, learning, and controlling their moods, and they become frustrated easily, none of which bodes well for success in school. Studies show that children with obstructive sleep apnea tend to be in the lower tenth percentile of their class. There is also a considerable overlap between the symptoms of attention deficit disorder (ADD) and obstructive sleep apnea.

Dreaming to breathe

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UNEASY

in the gut

Who likes talking about diarrhea?

Although it may not rank high in the Pleasant Dinner Conversation category, severe diarrhea is a serious side effect of diseases of the gut, a complex research area that is the focus of a group of top Alberta researchers.

"Actually, diarrhea is a good thing," Dr. Wallace MacNaughton explains matter-of-factly when the topic is broached. "Although having diarrhea can be nasty, it is actually doing us some good. It is the body's way of secreting water and electrolytes to help flush 'bad' bacteria out of the intestinal tract." Dr. McNaughton studies the epithelium, a thin layer of specialized cells that line the intestine and provide a critical barrier to keep bacteria from getting into the wall of the gut where inflammation may occur. Just as bathroom tiles in a shower help prevent water from seeping into the drywall beneath them, so do epithelial cells line up to ensure that bacteria stay within the intestine. Besides repelling bacteria this way, epithelial cells secrete water to speed them through the digestive tract. This is when diarrhea occurs.

A growing body of evidence is showing that inflammatory conditions in the gut may be caused by factors that reside there. Dr. MacNaughton and his colleagues at the University of Calgary are conducting pioneering research on the gastrointestinal (GI) tract to find out why some people develop leaky gut and other "plumbing" problems and how inflammation plays a role in their development and recurrence.

There's a lot of real estate to cover to find out why some guts go bad. The GI tract (digestive system), which includes the area from the mouth to the anus, consists of eight metres of large intestine (known as the large bowel or colon) and small intestine (known as the small bowel), plus the esophagus, liver, and stomach. Each part of this efficient plumbing system has its own job to do. The small intestine digests and absorbs dietary nutrients and the large intestine absorbs water. They work with the liver and pancreas to process the food we eat and deliver its valuable resources where needed in the body.

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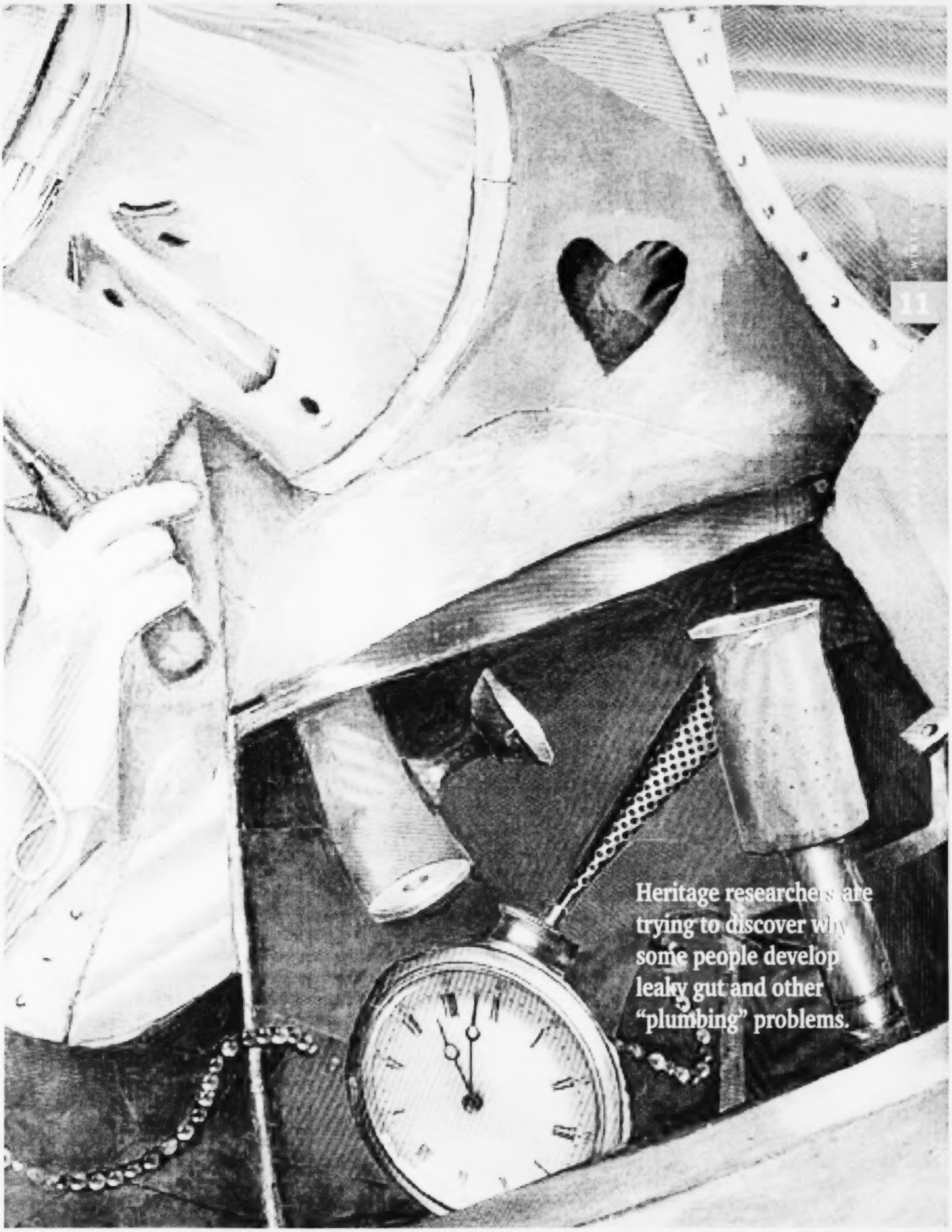


Heritage researchers are trying to discover why some people develop leaky gut and other "plumbing" problems.

Outnumbered but not outdone

There are 100 trillion bacteria in the body at any given time but only 10 trillion cells on hand to fight them. "Even though it is outnumbered 10 to 1, the body manages to cope quite handily with most bacteria," Dr. MacNaughton says. "The body gets along with bad bacteria as long as they are contained. It's when they get across the wall of the gut that they become a problem. That's why the epithelium is so important."

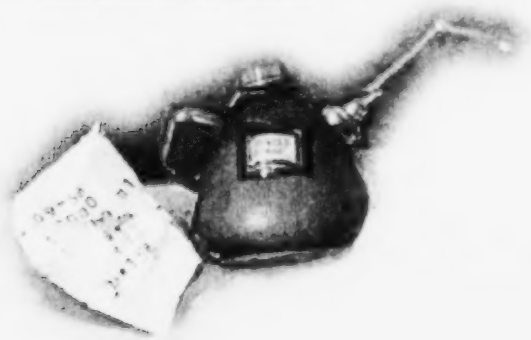
Dr. MacNaughton has so far determined that an overproduction of nitric oxide (NO), a molecule that works to kill bacteria, can stop epithelial cells from responding to another molecule that signals them to secrete water in response to bacteria. His lab has shown that a particular drug may help block the enzyme that produces NO and restore the water-secreting function of epithelial cells.

When epithelial cells don't work properly, the intestine becomes susceptible to infection and inflammation. This may be what happens in inflammatory bowel disease (IBD), a term used to describe two diseases of the intestines: ulcerative colitis and Crohn's disease. Alberta has one of the highest rates of IBD in the world.

Inflammation of the intestine manifests itself in many ways. The most common way is through diarrhea, but severe stomach aches, ulcers of the colon, and loss of fluid to the tissues are other symptoms related to IBD that can ravage a person's digestive system.

Gut reactions

Dr. MacNaughton's research goes hand in hand with the work of Dr. Jon Meddings. He also studies the events that lead to inflammation in the gut, working on the theory that increased epithelial permeability (leakiness of the intestine) is a major contributing factor to Crohn's disease. Although Crohn's disease is caused by unknown bacteria and viruses, environmental factors and genetics may play a role in the emergence of the disease.



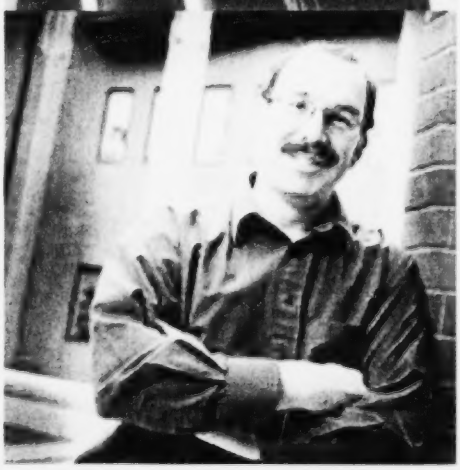
feeling

Dr. Meddings is testing whether leaky guts ultimately lead to Crohn's disease. He measures permeability in people in high-risk groups: those with relatives who already have the disease. "We've found that we can predict 60 to 80% of recurrences of Crohn's disease by measuring an increase in permeability up to two months before they get a flare-up," he comments. Permeability is measured by means of a simple test: "We put several types of sugar that don't normally digest into a glass of Kool-Aid," Dr. Meddings explains. "If the gut is leaky when they are consumed, the sugars will leak out and be excreted in the urine. We then measure sugar levels in the urine to determine the extent of permeability."

The Meddings lab has just completed a number of experiments that clearly demonstrate how leaky the intestine can be. "I used to think that increased permeability was probably a genetic marker, but I've seen enough data from other labs now that I actually suspect that it's a marker of having a certain population of bugs in your gut," Dr. Meddings says. The fact that more than one family member can get Crohn's disease may be due to the environment they share rather than the genes they have in common. He points to another commonality of Crohn's disease that adds strength to this line of thinking. "If you look at the spouses of people who have Crohn's disease, you find that a significant number of them also have increased permeability in the gut. This may suggest that there is an environmental influence, perhaps a shared bug that sits in the gut that causes all of this. We don't yet know for sure."

Plugging the leaks

In Edmonton, researcher Dr. Karen Madsen is testing a special mix, which plugs the tiny holes in the gut that can make it so permeable. The mix is made up of "good" bacteria that coat the gut like a thick white paste, protecting the outside of cells from bad bacteria. If it works, the paste could help soothe the effects of inflammation. Clinical trials of the paste begin in March 2001. Epithelial cells are also another focus of Dr. Madsen's research. She is investigating ways to stop the enzyme PARP, found in the nucleus of all cells and activated by DNA damage from using up the energy that epithelial cells need to keep their membranes closed. If she can stop PARP activity in epithelial cells, it would help stop leaking in the intestinal tract.



Although diarrhea is nasty, it is nature's way of flushing "bad" bacteria out of the gut.

The gut's mini-brain

Back at the University of Calgary, Dr. Keith Sharkey explains that the gut is unique because its enteric nervous system acts like a mini-brain controlling day-to-day processes within the intestine. "While the gut is certainly under the control of the brain in your head, it is well positioned to deal with issues that arise within its territory and use its 'brain' to control situations such as inflammation," he says. Although the role this system plays in the development of inflammation is still undefined, what is known is that many of the symptoms of IBD occur as a result of changes in the way the enteric nervous system works. One of the early effects of inflammation is the activation of the nerves located in the wall of the gut. Dr. Sharkey and other researchers have shown that although they help control inflammation, gut nerves can be corrupted physically and chemically through an infiltration of inflammatory cells that changes their structure.

In a new line of research Dr. Sharkey is focusing on cells called glia that surround gut nerves. It has recently been found that these cells are active during inflammation. They divide in response to it in the same way that glia in the brain respond to injury. "It may well be that the effects we're attributing to the gut nerves may actually be due in part to what's going on with the glia," he says. "For the next few years, we'll be studying the glia very intensively, along with the enteric nervous system to find out how they are involved in inflammation." Heritage student Yasmin Nasser will also be a key part of these studies for the Sharkey lab.

Targeting inflammation

Probably the worst part of IBD for most people with the disease is dealing with the pain caused by inflammation. While most people take anti-inflammatory drugs to relieve pain, drugs of this type can actually worsen IBD. They are known to prevent heart disease and stroke, but they can also damage the stomach and cause other side effects in some people if taken regularly.

With a lack of effective drug treatments for IBD out there, the research at another U of C lab may bring relief to those in need. Part of the work Dr. John Wallace does involves identifying chemical targets for pain-relieving drugs he helps develop. "I'm not specifically targeting inflammatory cells to develop anti-inflammatory drugs," he explains. "I'm targeting the chemical messengers that are responsible for bringing those cells to the site of inflammation." While Dr. Wallace is careful to mention that the drugs he works on won't cure inflammatory diseases, it is hoped they will offer pain relief with fewer damaging side effects.

FROM TOP: DR. WALLACE MACNAUGHTON, DR. JON VEDDINGS, DR. KAREN MADSEN, DR. KEITH SHARKEY

Indigenous people of the Amazon use the sap of the croton tree to treat stomach pain.

The source of the Amazon

Searching out sources of relief for inflammation has led to a unique research project for Dr. Wallace. He is testing the scientific properties of a tree sap that has been used in the Amazon for centuries to treat pain, skin wounds, and inflammation of the gastrointestinal tract. The sap comes from fast-growing croton trees found throughout the Amazon. He heard about it from a Peruvian student working in another lab.

Indigenous peoples of the Amazon dilute the sap and make a drink to treat stomach pain. Dr. Wallace thinks the properties in the sap could also help people with bad guts. "We're trying to identify the active ingredients in the sap and how they work," he explains. "We've had some success in identifying a mechanism in it that blocks a nerve receptor that transmits the pain signal."

The sap may work on inflammation in many forms. In a successful clinical trial, Dr. Wallace and colleagues in New York State have tested a balm they made from the sap that seems to quickly stop the itch from mosquito bites. "We tested it on pest-control workers in Louisiana and they found relief from a whole variety of insect bites," he says.

Collaborating broadens research scope

Over the years, the University of Calgary has built one of the best GI centres in the country. One of the hallmarks of its success is the strong collaboration between clinical scientists and basic researchers such as Drs. Sharkey, MacNaughton, Wallace, and Meddings. "We have three research groups that are specifically interested in inflammatory diseases within the gut," says Dr. Meddings. "That's a huge advantage over a lot of institutions where that doesn't exist." And it's a powerful combination that should maintain the University's standing in this research area and help move science closer to effective treatments and cures for diseases of the digestive system.

Dr. Wallace MacNaughton is a Heritage Scholar, an Associate Professor in the Department of Physiology and Biophysics, and a member of the Mucosal Inflammation Research Group in the Faculty of Medicine at the University of Calgary. He receives additional funding from the Canadian Institutes of Health Research (CIHR) and the Crohn's and Colitis Foundation of Canada.

Dr. Jon Meddings is a Heritage Senior Scholar and a Professor in the Department of Internal Medicine in the Faculty of Medicine at the University of Calgary. He receives additional support from the Canadian Institutes of Health Research (CIHR) and the Crohn's and Colitis Foundation of Canada.

Dr. Karen Madsen is a Heritage Scholar and an Assistant Professor in the Division of Gastroenterology in the Department of Medicine in the Faculty of Medicine and Dentistry at the University of Alberta.

Dr. John Wallace is a Heritage Scientist and a Professor in the Department of Pharmacology and herapeutics in the Faculty of Medicine at the University of Calgary. He receives additional support from the Canadian Institutes of Health Research (CIHR), the Crohn's and Colitis Foundation of Canada, and the Heart and Stroke Foundation of Canada.

Dr. Keith Sharkey is a Heritage Senior Scholar and a Professor in the Department of Medicine and the Department of Physiology and Biophysics in the Faculty of Medicine at the University of Calgary.

Recent publications:

Freeman SL, MacNaughton WK. Ionizing radiation induces iNOS-mediated epithelial dysfunction in the absence of an inflammatory response. *American Journal of Physiology* 2000; 278: G243-G250.

Jijon H, Churchill T, Malfair D, Wessler A, Jewell L, Parsons H, Madsen K. Inhibition of poly(ADP-ribose) polymerase attenuates inflammation in a model of chronic colitis. *American Journal of Physiology–* Gastrointestinal Liver Physiology 2000; 279: G641- G651

Meddings JB, and Swain MG. Environmental Stress Induces a Generalized Increase in Gastrointestinal Permeability Mediated by Endogenous Glucocorticoids in the Rat. *Gastroenterology* 2000, 119: 1019-1028

Sharkey K, Kroese ABA. Consequences of intestinal inflammation on the enteric nervous system: neuronal activation induced by inflammatory mediators. *Anatomical Record* 2001, 262: 79-90.

Wallace JL, McKnight W, Reuter BK, Vergnolle N. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. *Gastroenterology* 2000; 119: 706-714.

ABOVE: DR. JOHN WALLACE

GUT

Caring for our seniors

Barring a fatal accident or a terminal illness, all of us will grow old. How will we, our family and our doctors decide what care is appropriate when we need it?

That's just one of the questions being addressed by Lethbridge medical researchers Dr. Paul Hasselback and Dr. Chris Armstrong-Esther, in one of the largest studies of formal home care and informal caregiving in Alberta. Since the fall of 1998, the co-principal investigators and the Chinook Health Region's team have been tracking the care received by 330 elderly people in the predominantly rural southern Alberta area. The study group includes 180 seniors (about 55%), who had informal caregivers when the research began.

"Seniors are a high priority for this particular region," says Dr. Hasselback, Chinook's Medical Officer of Health. "We are keenly interested in trying to ensure that individuals are residing in the most appropriate environment for them." Much of government policy regarding care for the elderly is based on the crucial role of unpaid, informal caregivers such as family and friends, says Dr. Armstrong-Esther, Professor of Health Sciences at the University of Lethbridge. "There's a clear cost benefit to the government by keeping [the elderly] in the community," rather than in an institution.

However, restructured families, more women working away from home and other societal changes may mean far fewer informal caregivers in the future, unless the formal health-care system provides them with more support, Armstrong-Esther says. The researchers are investigating the type and intensity of care received, the role of the informal caregiver, factors that lead to institutionalization, as well as the health, quality of life, and economic outcomes among the elderly and their families who remain at home.

A home-care nurse involved with each study participant does three standardized assessments of the client 12 to 16 months apart. Data is collected on each person's physical needs, support services, physical and mental capacities and outcome.

The 1998 assessment studied 257 women and 73 men, whose mean age was 85.2; the 1998 assessment. The following year, there were 228 women and 60 men, with a mean age of 85.5.

"We've had deaths, we've had people who have gone into long-term care facilities," Hasselback says.

A preliminary comparison of the 1998 and 1999 assessments indicates that 30% of the participants showed increasing impairment of mental capacities between the two rounds. An elderly person's deteriorating mental state puts added stress on the informal caregiver, and Armstrong-Esther says it is often the reason why people are admitted to institutional care.

Stress levels among the informal caregivers, whose mean age was 63.2 years, did increase between the 1998 and 1999 assessments. Despite the changing role of women in society, 125 of these caregivers were female while only 55 were male; 45% were daughters, and 28% were spouses.

The study will yield a wealth of information and assessment tools that can be used within Alberta's regionalized home-care system, Hasselback says. "Managers of home care, I think, are going to find the information very useful."

The project is supported by the Health Research Fund, administered by AHFMR on behalf of Alberta Health and Wellness. The Chinook Health Region is a supporting agency.

Upcoming publication:

Armstrong-Esther C, Smith C, Snelgrove S, Clark DJ. Is there a future for informal care in a changing society? *Quality in Aging: Policy, Practice and Research* (Journal of the British Association for Services to the Elderly). Manuscript submitted for publication.

If you're allergic to cats, or know someone who is, you'll probably recognize this scenario: *You visit your cat-loving friends and almost immediately start wheezing. You're forced to leave as your asthma attack worsens, and soon you're breathing easily. But, six to nine hours later, you start wheezing again. Did someone bring a cat into the house?*

Not necessarily, says Dr. Redwan Moqbel, an international authority on asthma and a member of the Pulmonary Research Group at the University of Alberta. He explains that the allergic response in asthma is complex. There's the immediate response, which is caused by a type of antibody known as IgE. For years, IgE and mast cells were considered the major asthma villains, but not anymore. Now we know there's a lot more going on.

Taking the *wind* out of asthma

What is asthma?

Asthma is a chronic disease in which the breathing tubes of the lungs become inflamed, swollen and very twitchy, making it difficult to breathe. Mucus can also clog some of the airways, further hampering air exchange and trapping stale air in the lungs. Asthma is triggered by a complex array of such factors as allergies, exercise, viral infections, as well as emotions, including stress—although it is not a psychological disease.

"The response that occurs hours after exposure is regulated by a type of white blood cell called the eosinophil," explains Dr. Moqbel. "Eosinophils come out of the bone marrow, enter the blood, and make their way to the airways. There, they wreak havoc by releasing certain proteins which kill the cells that line the airways. This whole process takes awhile; thus, the time delay for the reaction."

Over time, after prolonged periods of inflammation, eosinophils damage the airway tissue and the thickened airway walls no longer react to medication, such as corticosteroids, which had previously been effective at reducing the airway inflammation.

Eosinophils aren't all bad. Their natural role is to protect us from parasitic worms. However when they turn their wrath against our own cells, the mechanism backfires.

Dr. Moqbel's research team has played an important role in illuminating exactly how eosinophils do this damage. Besides releasing proteins which damage cells, eosinophils can also make, store and secrete a number of key mediators of inflammation, called cytokines and chemokines. These regulate the activity of the eosinophils themselves, as well as other cells.

"The aim in my research is to understand the regulatory mechanism that controls the release of these mediators by eosinophils," says Dr. Moqbel. "Other researchers have looked at methods of preventing eosinophils from ever getting to the airways. My philosophy is that the presence of eosinophils isn't the problem; the problems start when they're activated. I'm convinced that understanding how activation is regulated will lead us to ways that prevent eosinophils from damaging tissue."

Dr. Moqbel is working in a number of areas to decipher regulation. One approach involves looking at how the mediator molecules stored in the granules inside the mediator cell actually get out. A certain complex of molecules on the outer surface of the granule must "dock" with a complementary complex (called a SNARE) on the inner surface of the cell membrane. Dr. Moqbel describes the process as "locking hands". Successful docking will allow secretion from the granule.

Having identified the mechanism of secretion, the lab has now turned its attention to finding ways to block it. Tetanus and botulinum toxins will both

inhibit the action of the locking molecules. Dr. Moqbel is pursuing this research with Dr. Paige Lacy and Heritage Medical Scientist Dr. Chris Bleackley. Their work has application beyond eosinophils because any cell that secretes membrane-bound proteins uses these molecules.

Another area of research is a family of proteins call tetraspanins. It is believed that these proteins facilitate the movement of proteins inside the eosinophil cell. One tetraspanin, CD63, is found on the membrane of granules. Experiments done in Dr. Moqbel's lab found that when eosinophils are stimulated by cytokines, the CD63 moves rapidly to the outer edges of the cell.

Here in Alberta, we have the capacity to make a significant contribution to asthma treatment.

"We have evidence that this translocation correlates with release of mediators," says Dr. Moqbel. "This is important because CD63 may be a marker for all eosinophil activation. It may be possible to take blood from an asthmatic and, by measuring the CD63, know the exact state of the person's disease."

Work is also progressing on understanding the production of oxidants by eosinophils. These molecules are deadly; they are responsible for a large proportion of the cell damage caused by eosinophils. Dr. Moqbel's team has identified certain enzymes and chloride channels that are involved in oxidant release.

"So we're approaching the regulation of mediator release from eosinophils from three different perspectives," says Dr. Moqbel. "Effective inhibition will probably require a combination of these.

"Our goal is to block the secretory pathways in eosinophils, and we're very focused on making sure that our research is relevant to clinical application. Our job is not only to publish scientific papers: We must truly tackle the issue of asthma."

For good reason. Asthma ranks among the most common chronic conditions in Canada. More than 50,000 Canadians are admitted to hospital with asthma-related problems every year. The incidence of asthma has been increasing over the past 20 years, especially among children. It is estimated that about $1billion per year is spent on asthma treatment in Canada.

"Here in Alberta, we have the capacity to make a significant contribution to asthma treatment," says Dr. Moqbel. "We have a very powerful set-up at the University of Alberta with the Pulmonary Research Group, the Asthma Clinic, other collaborations with scientists in Biochemistry, Pharmacology and Medicine.

Are we too clean?

The incidence of asthma is increasing throughout the Western world. Why? A recent hypothesis suggests that we've diverted the immune response that protects us from an allergic-type reaction to bacterial infections.

"Many people have speculated that this is the result of living in too hygienic an environment," says University of Alberta asthma researcher Dr. Redwan Moqbel. "We've eliminated or reduced the bacteria that our immune system is designed to fight. The immune system's 'normal' pattern of fighting infection is known as the Th1 pattern. Asthmatics show a different kind of response, called Th2. It's as if their immune system has been switched to do something else.

"Some researchers are developing new strategies to divert the immune system of asthmatics back to the Th1 pattern."

The "Th" in Th1 and Th2 patterns stands for "T helper" cells, key components of our immune system. Before Dr. Moqbel came to Alberta, he was on the team (based at the National Heart and Lung Institute in London, England) which introduced the concept that T cells regulate the asthmatic response.

"When I teach my students about asthma, I use slides that clearly show the magnitude of damage caused by eosinophils. I know we can find a way to stop this damage from occurring. This must be our goal."

Dr. Redwan Moqbel is a Heritage Senior Medical Scholar and an Associate Professor in the Department of Medicine at the University of Alberta. His research is supported by the Canadian Institutes for Health Research, CIHR/Rx&D Research Program, the Alberta Lung Association, the University of Alberta Hospital Foundation, The Francis Families Foundation, Glaxo Wellcome–Inc. Canada, Aventis, and IMMS (Mexico).

Recent publication:

Lacy P, Mahmudi-Azer S, Bablitz B, Hagen SC, Velazquez JR, Man SFP, Moqbel R. Rapid mobilization and release of intracellularly stored RANTES in response to interferon-g in human eosinophils. *Blood* 1999; 94: 23-32.

Review article:

Moqbel R, Lacy P. Eosinophils. *Allergy and Allergic Diseases: The New Mechanisms and Therapeutics*, ed. J Denburg. Totowa, NJ: Humana Press Inc., 1998. Chapter 8, 139-165.

wind

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Over time, after prolonged periods of inflammation, eosinophils damage the airway tissue and the thickened airway walls no longer react to medication, such as corticosteroids, which had previously been effective at reducing the airway inflammation.

Eosinophils aren't all bad. Their natural role is to protect us from parasitic worms. However when they turn their wrath against our own cells, the mechanism backfires.

Dr. Moqbel's research team has played an important role in illuminating exactly how eosinophils do this damage. Besides releasing proteins which damage cells, eosinophils can also make, store and secrete a number of key mediators of inflammation, called cytokines and chemokines. These regulate the activity of the eosinophils themselves, as well as other cells.

"The aim in my research is to understand the regulatory mechanism that controls the release of these mediators by eosinophils," says Dr. Moqbel. "Other researchers have looked at methods of preventing eosinophils from ever getting to the airways. My philosophy is that the presence of eosinophils isn't the problem; the problems start when they're activated. I'm convinced that understanding how activation is regulated will lead us to ways that prevent eosinophils from damaging tissue."

Dr. Moqbel is working in a number of areas to decipher regulation. One approach involves looking at how the mediator molecules stored in the granules inside the mediator cell actually get out. A certain complex of molecules on the outer surface of the granule must "dock" with a complementary complex (called a SNARE) on the inner surface of the cell membrane. Dr. Moqbel describes the process as "locking hands". Successful docking will allow secretion from the granule.

Having identified the mechanism of secretion, the lab has now turned its attention to finding ways to block it. Tetanus and botulinum toxins will both

inhibit the action of the locking molecules. Dr. Moqbel is pursuing this research with Dr. Paige Lacy and Heritage Medical Scientist Dr. Chris Bleackley. Their work has application beyond eosinophils because any cell that secretes membrane-bound proteins uses these molecules.

Another area of research is a family of proteins call tetraspanins. It is believed that these proteins facilitate the movement of proteins inside the eosinophil cell. One tetraspanin, CD63, is found on the membrane of granules. Experiments done in Dr. Moqbel's lab found that when eosinophils are stimulated by cytokines, the CD63 moves rapidly to the outer edges of the cell.

Here in Alberta, we have the capacity to make a significant contribution to asthma treatment.

"We have evidence that this translocation correlates with release of mediators," says Dr. Moqbel. "This is important because CD63 may be a marker for all eosinophil activation. It may be possible to take blood from an asthmatic and, by measuring the CD63, know the exact state of the person's disease."

Work is also progressing on understanding the production of oxidants by eosinophils. These molecules are deadly; they are responsible for a large proportion of the cell damage caused by eosinophils. Dr. Moqbel's team has identified certain enzymes and chloride channels that are involved in oxidant release.

"So we're approaching the regulation of mediator release from eosinophils from three different perspectives," says Dr. Moqbel. "Effective inhibition will probably require a combination of these.

"Our goal is to block the secretory pathways in eosinophils, and we're very focused on making sure that our research is relevant to clinical application. Our job is not only to publish scientific papers: We must truly tackle the issue of asthma."

For good reason. Asthma ranks among the most common chronic conditions in Canada. More than 50,000 Canadians are admitted to hospital with asthma-related problems every year. The incidence of asthma has been increasing over the past 20 years, especially among children. It is estimated that about $1billion per year is spent on asthma treatment in Canada.

"Here in Alberta, we have the capacity to make a significant contribution to asthma treatment," says Dr. Moqbel. "We have a very powerful set-up at the University of Alberta with the Pulmonary Research Group, the Asthma Clinic, other collaborations with scientists in Biochemistry, Pharmacology and Medicine.

The incidence of asthma is increasing throughout the Western world. Why? A recent hypothesis suggests that we've diverted the immune response that protects us from an allergic-type reaction to bacterial infections.

"Many people have speculated that this is the result of living in too hygienic an environment," says University of Alberta asthma researcher Dr. Redwan Moqbel. "We've eliminated or reduced the bacteria that our immune system is designed to fight. The immune system's 'normal' pattern of fighting infection is known as the Th1 pattern. Asthmatics show a different kind of response, called Th2. It's as if their immune system has been switched to do something else.

"Some researchers are developing new strategies to divert the immune system of asthmatics back to the Th1 pattern."

The "Th" in Th1 and Th2 patterns stands for "T helper" cells, key components of our immune system. Before Dr. Moqbel came to Alberta, he was on the team (based at the National Heart and Lung Institute in London, England) which introduced the concept that T cells regulate the asthmatic response.

"When I teach my students about asthma, I use slides that clearly show the magnitude of damage caused by eosinophils. I know we can find a way to stop this damage from occurring. This must be our goal."

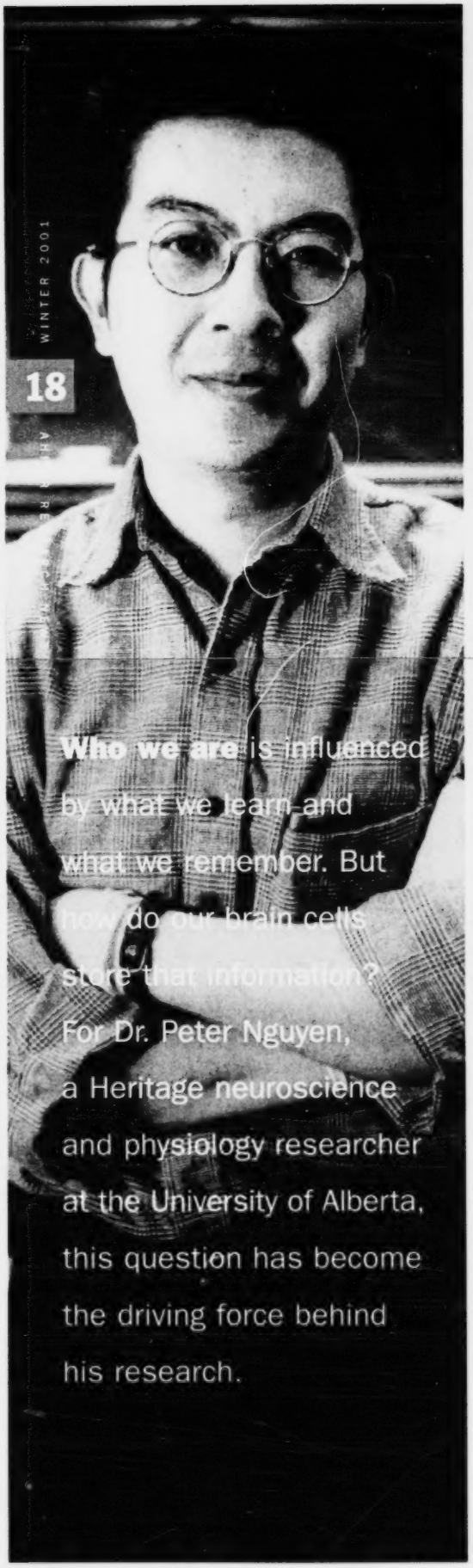
Dr. Redwan Moqbel is a Heritage Senior Medical Scholar and an Associate Professor in the Department of Medicine at the University of Alberta. His research is supported by the Canadian Institutes for Health Research, CIHR/Rx&D Research Program, the Alberta Lung Association, the University of Alberta Hospital Foundation, The Francis Families Foundation, Glaxo Wellcome–Inc. Canada, Aventis, and IMMS (Mexico).

Recent publication:

Lacy P, Mahmudi-Azer S, Bablitz B, Hagen SC, Velazquez JR, Man SFP, Moqbel R. Rapid mobilization and release of intracellularly stored RANTES in response to interferon-g in human eosinophils. *Blood* 1999; 94: 23-32.

Review article:

Moqbel R, Lacy P. Eosinophils. *Allergy and Allergic Diseases: The New Mechanisms and Therapeutics*, ed. J Denburg. Totowa, NJ: Humana Press Inc., 1998. Chapter 8, 139-165.



Who we are is influenced by what we learn and what we remember. But how do our brain cells store that information? For Dr. Peter Nguyen, a Heritage neuroscience and physiology researcher at the University of Alberta, this question has become the driving force behind his research.

"Learning is the acquisition of knowledge, memory is the retention of knowledge over time. Both are critical in our lives–from something as mundane as remembering your PIN for the bank machine to something really important like finding your way home after work," says Dr. Nguyen.

Learning and memory has been a hot research topic for many years. There has been substantial progress from a variety of fields including physiology, pharmacology, molecular biology, genetics and behavioural science.

"What goes on in the brain is incredibly complex," says Dr. Nguyen. "Deciphering the mechanisms of cognition is going to take a combination of approaches involving collaboration among many researchers. This is exactly what is happening right now."

By understanding how memories are made, scientists may one day develop therapies that slow the decline of memory in old age, prevent the terrible memory loss of Alzheimer's disease, and perhaps even erase traumatic memories.

Memories *are made of this*

Inside the brain

The human brain is made up of billions of nerve cells called neurons. Electrical impulses produced by neurons trigger the release of chemical transmitters at synapses (the connection points between neighbouring nerve cells). The process by which neurons communicate with each other is known as synaptic transmission. It is vital for memory formation.

Neurons can change the strength of transmission at their synapses, in response to alterations in their electrical activity. This is called "synaptic plasticity", and researchers like Dr. Nguyen believe it underlies cognitive processes such as learning and memory. One form of synaptic plasticity involves an enhancement (the technical term is potentiation) of synaptic transmission, which may be important in certain types of information processing crucial for memory formation.

"Synaptic plasticity may be altered as we grow old, and this may explain the changes in memory that occur with aging," adds Dr. Nguyen.

The signals to memory

Signaling enzymes are known to modulate synaptic transmission during learning. These enzymes, called protein kinases and phosphatases, are found in neurons located in parts of the brain that are critical for memory formation. They regulate the activity of key proteins, which in turn may play important roles in synaptic plasticity and memory consolidation. In Dr. Nguyen's lab, the main interest is in identifying and characterizing the signaling pathways that are key to the formation of enduring memories.

Nerve cells exhibit an astonishing range of electrical activity. They can fire electrical impulses once per minute, or 100 times a second. "Figuring out which patterns of electrical activity can recruit specific intracellular pathways is critical. This may enable us to link the activation of these signaling pathways to certain types of synaptic plasticity and memory," says Dr. Nguyen.

His lab is also trying to figure out which pathways may change with aging, and whether altered signaling in the brains of older animals can directly influence memory function and synaptic plasticity.

Forgetting the way

In collaboration with researchers at the University of Pennsylvania, Dr. Nguyen's team uses genetically altered mice that have reduced brain levels of a key protein kinase (cAMP-dependent protein kinase, or PKA). As a result, short-term memory is maintained but long-term memory is impaired. Although the mice can learn their way through a maze, they will no longer remember the way 24 hours later.

The researchers study how synaptic transmission is changed in the brains of these genetically modified mice. They are trying to find out whether PKA is tuned to particular patterns of electrical activity. This will shed light on the physiological activation properties of this enzyme in the context of synaptic and cognitive functions.

"The transmission between nerve cells is less efficient in our genetically altered mice," says Nguyen. "Synaptic transmission is harder to enhance for longer periods of time in these mice. Their synapses are unable to maintain an enhanced level of transmission. Enhancement of communication between nerve cells may be crucial for learning and remembering new pieces of information. We are trying to find out what exactly causes this failure to maintain enhanced transmission. Are other proteins involved, ones that are critically dependent on activation of PKA?"

A future challenge will be to link the molecular ballet occurring at synapses to actual animal behaviour. "There's always been a substantial gap in our understanding of how the molecular mechanisms of synaptic plasticity can directly account for behaviour and for cognitive processes such as learning and memory," says Dr. Nguyen.

"Because neuroscience is multidisciplinary in nature, this gap is beginning to narrow. Experts in animal behaviour are collaborating with neurophysiologists like myself. This is absolutely essential. There's still a long way to go before we understand learning and memory completely, but there are a lot of reasons to be optimistic. We have the tools to examine the machinery of the synapse and also that of the mind through molecular biological, electrophysiological and behavioural approaches.

"I doubt that a single molecule or pathway is the key to understanding learning and memory. But once we know more about these signaling pathways and how they are altered by activity, aging, or disease, then we can look for strategies that may enhance the beneficial alterations and minimize the harmful ones. We may be able to enhance or suppress signal transmission at the synapse by the use of certain drugs or through other molecular means, and thereby alleviate some severe memory deficits." fn

Dr. Peter Nguyen is a Heritage Medical Scholar and an Assistant Professor in the Department of Physiology in the Faculty of Medicine and Dentistry at the University of Alberta. He is a Canadian Institutes for Health Research (CIHR) New Investigator. Working with Dr. Nguyen are AHFMR Fellow Steven Duffy, AHFMR student Newton Woo, and graduate student Jennie Young.

Review article on learning and memory:
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A stimulating read

Put it down to a textbook. It was the written word that inspired Peter Nguyen to pursue a research career in neurophysiology.

"I was in third year, taking a neurobiology course at the University of Toronto," recalls Dr. Nguyen. "The text-book (*From Neuron to Brain* by Stephen Kuffler) was wonderful. It didn't simply summarize the basic principles, it described the experiments leading up to these conclusions. The text was able to communicate the excitement of exploration. It stimulated my interest in laboratory research.

"Now, in the experiments that we do in my lab, one can actually see electrical signaling between nerve cells. Electrophysiology is very immediate and 'on-line'. It's an exhilarating endeavour, even when experiments fail, which is 90% of the time!

"Another satisfying aspect of running a lab is seeing undergraduate and graduate students flourish. Quality undergraduate teaching, inside and outside the lab, is vital to stimulating interest in this field."

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Award-winning student

Scholarship and mentorship

For the past four years Elaine has been focusing her research on how changes in calcium or nucleotide levels in cells affect the way calreticulin works. She is a Ph.D. biochemistry student in Heritage researcher Dr. Marek Michalak's lab. Dr. Michalak has spent a decade researching the effect on muscle of the cell-membrane protein. He showed that during embryo development calreticulin plays a critical role in helping muscle develop properly. His recent findings could provide a way to intervene early in heart disease.

McLeod honour

Originally from Limerick, Ireland, Elaine came to the University of Alberta in Edmonton "because I heard there was a good opportunity to do good research here and that it would be well-supported through AHFMR," she says. Her "good research" recently landed Elaine the 2000 Lionel E. McLeod Health Research Scholarship. The award is given out by the Foundation to an exceptional student from the University of Alberta, Calgary, or British Columbia who shows outstanding promise in human health research. The award honours the late Dr. Lionel McLeod, who was the first President of AHFMR, President and Chief Executive Officer of the University Hospital in Vancouver, Dean of Medicine at the University of Calgary, and Head of Endocrinology at the University of Alberta.

I heard there was a good opportunity to do good research in Edmonton.

Research beginnings

Reflecting on her background Elaine says she did well in biology and chemistry as a young girl and that prompted her to study medical lab sciences after high school. It was as a third-year student rotating through different disciplines in a hospital lab that Elaine realized she wanted a more active role in research. She went on to complete an honours undergraduate degree in biomedical sciences to further that goal.

With a Ph.D. nearly in hand and a post-doctoral fellowship in either Toronto or Montreal on offer, it looks as if Elaine will grant herself another wish. She plans to use her budding research career as a way to see the world. Her future plans include working for a pharmaceutical or biotechnology company that she hopes will give her even more chances to travel.

Elaine Corbett is an AHFMR student at the University of Alberta working in the lab of Heritage Scientist Dr. Marek Michalak.

Recent publication:

Corbett EF, Michalak KM, Oikawa K, Johnson S, Campbell ID, Eggleton P, Kay C, Michalak M. The confirmation of calreticulin is influenced by the endoplasmic reticulum luminal environment. *Journal of Biological Chemistry* 2000; 275 (35): 27177-27185.

reader resources

Research Views

Canadian Council on Animal Care
http://www.ccac.ca/english/welcome.htm

Fear of falling

National Center for Injury Prevention and Control
http://www.cdc.gov/ncipc/factsheets/fallcost.htm

University of Lethbridge
http://home.uleth.ca/

A deadly delivery

Cell (science journal)
www.cell.com

University of Alberta
Department of Biochemistry
www.biochem.ualberta.ca

Exploring breathing control in infants

National SIDS Resource Center
http://www.circsol.com/sids/

Helping children to get a good night's sleep, and

Taking the wind out of asthma

Alberta Lung Association
Toll Free: 1-800-931-9111
Health Ed Line: 1-800-661-LUNG
http://www.ab.lung.ca/

Alberta Asthma Centre
http://www.asthmacentre.org/

An uneasy feeling in the gut

Crohn's and Colitis Foundation of Canada
Alberta and the Northwest Territories regional office: 1-888-884-2232
www.ccfc.ca

Northwestern Society of Intestinal Research
www.badgut.com

Caring for our seniors

Health Canada: Aging and seniors
http://www.hc-sc.gc.ca/seniors-aines/

Calgary Regional Health Authority: Your health: Seniors health
http://www.crha-health.ab.ca/hithconn/topics/seniors.htm

Memories are made of this

Exploratorium
http://www.exploratorium.edu/memory/

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http://www.crha-health.ab.ca/hithconn/topics/seniors.htm

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Heritage Youth Researcher Summer Program

A summer to remember for Grade 11 students

The Alberta Heritage Foundation for Medical Research (AHFMR) is offering bright Grade 11 students who love science a six-week-long, paid summer research experience.

The Heritage Youth Researcher Summer (HYRS) Program will award up to 40 Grade 11 students from all over Alberta a summer job working with top-notch AHFMR-funded researchers at provincial universities. HYRS will deliver a hands-on experience of health research to students and introduce them to exciting career opportunities in the field. HYRS students will be asked to make a presentation about their experiences to a science class at their high school when they return to school in the fall.

HYRS: science teachers are the key

The HYRS Program needs the expertise of science teachers throughout the province to make it a success. Science teachers are asked to encourage students who meet the program qualifications to apply to HYRS.

During the summer, each HYRS student's refereeing teachers will be invited to join the student for a special Teachers Day. Participating teachers will spend time in a lab alongside their former students, be guests at an AHFMR-sponsored lunch, and learn about the latest advances in research from presentations by researchers.

HYRS: another great idea by AHFMR

For more information about the Heritage Youth Researcher Summer (HYRS) Program, please check our web site at **www.ahfmr.ab.ca** OR call Grace Ennis, HYRS Program Manager, Northern Alberta at **(780) 492-5348** or Nancy Whelan, HYRS Program Manager, Southern Alberta at **(403) 220-6617/7262** or **(403) 870-5556**. E-mail: **grace.ennis@ahfmr.ab.ca** or **nancy.whelan@ahfmr.ab.ca**

Application forms will be mailed to every high school at the end of February and will be available on our web site.

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Physicians: please place in your patient waiting rooms.